

## THE MODERN THERAPY OF SYPHILIS\*

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THE introduction of salvarsan by Ehrlich in 1910 marks the beginning of the modern era in the treatment of lues. Although the early hopes of being able to effect a cure by one *sterilisans magna* have been disappointed, yet the synthetic arsenicals have proved of inestimable value and now occupy the premier place in our anti-syphilitic armamentarium. Since the war a very large number of arsenical preparations have been placed on the market, and recently there have been many bismuth products, chiefly of French origin.

At the present time the differences of opinion regarding the best preparations to use and the methods and periods of their employment are most confusing. We find one clinic employing arsenicals once in one to three weeks, whereas another employs them every day or two; also we find differences of opinion regarding the particular preparation to be used. Some maintain that the original salvarsan or its copies are the most effective while others hold similar views concerning the neo group. Others again advocate still more modern preparations; sodium salvarsan; silver salvarsan; sulfarsenol; gelatin-arsphenamine, and a host of others. Also there are many, especially in Europe, among whom is L. W. Harrison, who think arsenical preparations are best given intramuscularly or subcutaneously, their contention being that the drug is absorbed and eliminated too rapidly when administered intravenously, making the treatment intermittent rather than continuous.

Regarding the comparative value of the various arsenical preparations we must consider:

(1) The therapeutic index, *i.e.* the relation of the curative to the toxic dose. (2) The convenience and safety of administration.

Schamberg, Kolmer and Raiziss<sup>1</sup> tested various preparations for toxicity and trypanocidal power. White rats inoculated with *trypanosoma equiperdum* were used. They found that for arsphenamine (American salvarsan) the therapeutic index

was 1:21; for neo-arsphenamine it was 1:22; for sodium-arsphenamine it was 1:10.

Strauss, Sidlick, Mallas and Crawford<sup>2</sup>, have investigated the action of silver-arsphenamine as compared with arsphenamine and neo-arsphenamine. Three groups of patients of 25, each averaging much the same as regards age, duration of disease, conditions of general health etc., were treated twice a week for four weeks with graded doses of these three drugs. The comparative value of each was determined by the Wassermann reaction one month after the completion of treatment. Of the 25 cases treated by arsphenamine 13 were serologically negative. Of the neo group 9 were negative, of the silver group only one was negative.

It would appear from the foregoing experiments and many others I have not space to mention, that arsphenamine and neoarsphenamine are much higher in trypanocidal power than sodium arsphenamine and silver arsphenamine.

All drugs of the salvarsan group are put on the market in the form of the hydrochloride, to insure their stability. They therefore must be neutralized before administration. This is accomplished by means of sodium hydrate. As salvarsan has a double molecule, (being built, as it were, around a double benzene ring) it is important that both HCl. groups should be replaced by sodium as, if only one is replaced the mono-sodium salt resulting is very toxic. Salvarsan must be given in a very dilute solution, usually not stronger than 1 in 200 normal saline. This necessitates a very large syringe or preferably, a gravity apparatus, and each injection takes a considerable amount of time.

The neo preparation is already neutralized; it is easily soluble in distilled water and can be given in a 10% solution in a small syringe either intravenously or intramuscularly, although the latter produces considerable local reaction. It is unfortunately not very stable and both its spirochaetocidal power and toxicity vary considerably, sometimes as much as 300% in different lots. It also oxidizes very quickly after being dissolved

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and exposed to the air. It must therefore be given immediately, so it is necessary to prepare each dose separately. At the same time it is a much more convenient drug to give than salvarsan, and as its therapeutic index is usually about the same it would appear to be the drug of choice for office use or for a small number of patients in a clinic. However, as it does not follow that the therapeutic index of a drug as ascertained by animal experimentation is the exact measure of its efficiency as a spirochaetocide in humans, and as the neo group is notoriously variable and unstable, there is a great deal to be said for the use of salvarsan, especially in clinics where a large amount is dissolved and neutralized at one operation and a considerable time may elapse before it is all administered.

Most of the arsenicals are too irritating for subcutaneous or intra-muscular administration, and the neo group, which are the least irritating of the older preparations, are as already mentioned extremely variable, and oxidize very rapidly. Recently, sulfarsenol and sulpharsphenamine have been introduced. These substances are isomeric and differ from neo-salvarsan chemically in having a higher proportion of oxygen, so that a better name would appear to be oxy-neo-arsphenamine. They are more stable and less irritating, so they may be given subcutaneously as well as intramuscularly or intravenously. Sulfarsenol is used quite extensively in the Royal Navy and seems to have as high a spirochaetocidal power as the other arsenicals; it is much easier to give and is more stable than the neo group. It can be given subcutaneously in a 20 to 30% solution.

According to Dr. Voegtlin of the U. S. Public Health Service the average minimum lethal dose of sulpharsphenamine is 400 mgms. per kilo. of body weight (white rats being the animals used for the test,) while the minimum effective dose is about 20 mgms. per kilo. so that the therapeutic index is 1 to 20 or about the same as arsphenamine and neo-arsphenamine. Used subcutaneously the minimum lethal dose was about 500 mgms. while the lowest effective dose was about 25 mgms., making it proportionately as effective as by the intravenous method.

Dr. Voegtlin also carried out comparative tests of arsphenamine, neo-arsphenamine and sulpharsphenamine the latter being given both intravenously and subcutaneously. White rats were injected with *trypanosoma equiperdum* and trypanosoma counts of the blood made at intervals for 30 days after treatment. The result of these

tests showed that sulpharsphenamine given subcutaneously had the higher percentage of cures.<sup>3</sup>

Another experiment was carried out on rabbits to determine the relative spirochaetocidal power of German neo-salvarsan and sulpharsphenamine. These rabbits were inoculated with Nicholi strain of *spirochaeta pallida* and after pronounced chancres had been produced some of the animals were given graded doses of neo-salvarsan intravenously and others graded doses of sulpharsphenamine subcutaneously. The lesions were examined for spirochaeta before treatment and all were found positive; they were examined again 24 hours after treatment and were all found negative. It is argued that sulpharsphenamine given subcutaneously is at least as effective as neo-salvarsan employed intravenously. There are also tables showing that the arsenic contained in sulpharsphenamine is more effective as a spirochaetocide than the arsenic contained in arsphenamine or neo-arsphenamine.

Another point to which attention is called is that the maximum trypanocidal effects of sulpharsphenamine occur three or four days after administration, whereas arsphenamine and neo-arsphenamine produce their maximum effects within 24 hours, the former thus producing fewer and less severe reactions and giving a more uniform and continuous medication.

*Gelatin Arsphenamine.*—The researches of Oliver, Yamada, and Kolos,<sup>4</sup> into the reduction of the toxicity of arsphenamine by combining it with the hydrophil colloids, especially gelatin, seem to show that toxicity is very much lowered by this means, the minimum lethal dose being increased from 10 gm. per kilo to 15 gm. per kilo, a reduction in toxicity of 33.1-3%. When arsphenamine is injected into the blood there occur the following changes.

1. Agglutination of the red blood corpuscles.
2. Hæmolysis.
3. Incoagulability of the blood, which results from the action of the drug on the fibrinogen.

In such animals the arsphenamine can be demonstrated analytically to be bound to the cells and plasma proteins. An animal may be killed by an enormous dose of gelatin arsphenamine, the death being due to circulatory failure, but in such animals none of the characteristics of physical toxicity can be demonstrated. A subsequent series of experiments by the same investigators showed that the trypanocidal power of gelatin arsphenamine was not diminished *pari*

*passu* with its toxicity but remained much the same as that of arsphenamine.<sup>5</sup>

These preparations, sulpharsphenamine and gelatin arsphenamine, have not as yet been tried out sufficiently for one to speak definitely concerning them, but if the later results are even approximately as good as those already obtained the treatment of syphilis bids fair to be revolutionized, being made simpler, quicker and safer and free from the lamentable accidents that sometimes follow intravenous administration of the preparations now generally in use.

*Tryparsamide.*<sup>6</sup>—The foregoing arsenicals are designed chiefly for use in the earlier stages of syphilis and are not so effective in late and nervous cases. A preparation called tryparsamide is being introduced by the Rockefeller Institute for Medical Research. This drug is the sodium salt of N-Phenyl-glycine-amide-p-arsonic acid. It has passed through the animal experimentation stage successfully and is now being used clinically by a few selected observers. The therapeutic index of this drug is comparatively low being only about one third that of arsphenamine or neo-arsphenamine. However, it owes its therapeutic effects to the power it possesses of permeating the tissues and reaching organisms that are beyond the reach of the ordinary arsenicals. It is therefore supposed to be very useful in late and neuro-syphilis and is said to produce excellent results in general paresis, which up to the present has not been amenable to any extent, to treatment by the arsenicals. In this disease there are large numbers of spirochaetes in the central nervous system and tryparsamide is supposed to have the power of reaching and destroying them. Another characteristic of this drug which has a rather important bearing upon its employment is that it causes increased weight and activity and improved general health, which is not the case with the arsenicals generally in use at present in the treatment of lues. It is usual to have patients lose considerable weight during a course of treatment and not recover it until the rest period.

*Mercury.*—With the use of mercury everyone is of course familiar so only a few words will be necessary here. The use dates back far into the middle ages although regular physicians did not employ it until the end of the 15th century. Nowadays it is given intramuscularly almost exclusively, excepting in very young children to whom it is given by inunction, and in those cases who refuse to have intramuscular injections,

when it may be given by inunction or intravenously. Soluble and insoluble preparations are used. Of the former the chloride, the iodide and succinamide, are mostly used, and of the latter the salicylate is most popular. The soluble salts must be given frequently, *i.e.*, every two days or so, owing to their rapid absorption and elimination and this is often very inconvenient for the patient owing to the frequent visits to the physician and the pain that often follows the injection. The salicylate can be given once weekly in 1 to 2 grain doses. The vehicle generally used is vegetable oils, with a certain amount of local anaesthetic such as chlorotone or creasote to allay the pain, which is generally not great, providing the injection is made actually into a muscle and not subcutaneously into the inter-muscular spaces where nerves and vessels may be encountered, or into dense fibrous tissue. Grey oil which is a preparation of metallic mercury is still often employed for intramuscular injection. In intravenous use Parke Davis & Co. manufactures mercurosal, a synthetic mercury compound which seems to produce good results, although it is as yet comparatively new.

*Potassium iodide.*—Potassium iodide was first used by Wallace of Dublin in 1834. It is not a spirochaetocide but is supposed to aid in the absorption of fibrous tissue, in fact it has been proved to cause the disappearance of gummatous tissue. As one of the earliest changes caused by the spirochaeta pallida is the formation of fibrous tissue, and the difficulty of curing old cases is probably largely due to the spirochaete being protected by a wall of fibrous tissue through which the spirochaetocidal drug cannot penetrate, it would seem reasonable to employ iodides in all cases of lues excepting perhaps the early primaries. It is not uncommon to see a primary sore heal under salvarsan only to break down if the treatment is discontinued, showing that all the organisms at the site of the lesion had not been destroyed by even several injections of the drug. Perhaps iodides would facilitate the destruction of these organisms; the also question of excision of primary sores arises in this connection. It would seem that the patient would at least be no worse off after the excision and might be a great deal better.

*Bismuth.*—Bismuth was first used in the treatment of syphilis by Masucci and Balzer in 1889 the proto-iodide being employed. Since then there has been a great deal of work done with this drug. At the present time there are a large

number of preparations on the market, the chief of these being trepol, neo-trepol, muthanol, quinby and also the colloidal bismuths such as bismuthoidal which can be given intravenously as well as intramuscularly, the latter being the method of employment for the others. It is claimed that bismuthoidal is less irritating, more easily absorbed and has greater spirochaetocidal powers than the others. At the Montreal General Hospital it has been found that a few Wassermann-fast cases have become negative after 10 or 12 injections of neo-trepol but for the most part the results have been disappointing, although it is too early to be able to form an opinion as to its ultimate value. It is not fair to assume that because every old Wassermann-fast case does not become negative after one course of bismuth, the drug is without value. The fact that even a few have become negative after one course seems to me to be very encouraging.

At the Montreal Dispensary I have had one case of long standing syphilis, with pain and weakness of the legs, positive blood Wassermann, and negative cerebro-spinal fluid. This man had been unable to do any work for months and was steadily getting worse in spite of treatment with novarsenobenzol, mercury and potassium iodide. He was put on bi-weekly intramuscular injections of neo-trepol and began to improve from the first. Before he had half finished his course he was back at work feeling as well as he had ever felt. He is still at work at the present and feeling well.

My colleague Dr. Conover reports a case of severe lightning pains of early tabes, which were completely stopped by one injection of neo-trepol. There seems to be a field for the employment of bismuth in the later stages of syphilis especially in Wassermann-fast cases which are hypersensitive to or do not respond to arsenic or mercury.

The question now arises how often are the arsenical preparations to be used and should mercury be given with them?

*Treatment at Mayo Clinic.*—There is the widest divergence of views on both of these points. In the Mayo Clinic for example, arsenobenzol is given every second day for four doses, in early cases, during which period the patient is kept in bed. He then leaves hospital and is given mercury intramuscularly for 5 weeks (mercury succinamide five doses per week and mercury salicylate one dose per week). This is followed by one week's rest without treatment, after which

a second course is given, the same as the first, and so on. Needless to say this is very heroic treatment and patients must be closely watched for complications. Many patients have declared that they would rather have the disease than the cure.

*Treatment at the Montreal General Hospital.*—Here mercury salicylate is given intramuscularly during the arsenical (diarsenol) course. The first course of treatment (the intensive course) is given every week, diarsenol on the 1, 3, 6, 9, 12 and 15th weeks, and mercury salicylate on the 2, 4, 5, 7, 8, 10, 11, 13 and 14th weeks.

Commander Scott who is the genito-urinary expert of the Mediterranean Fleet states<sup>7</sup>: "When we compute an arsenical course at 4 grammes it is not because we consider this enough in all cases but because we do not consider it safe to give more. Arsenic taxes both the liver and kidneys and we know that mercury can damage the latter. If the excretory system is inefficient arsenic becomes dangerous. If mercury is given arsenic must be reduced, and as the latter is infinitely more powerful as a spirochaetocide such reduction is illogical. Why fiddle about with bad tools when better are available? For the same reason mercury should not be employed between arsenical courses—this period is for rest. It is most undesirable to plant a second arsenical course on a wearied excretory system." He goes on to say: "If a course of 4 grammes is spread over such a long period as 14 weeks it is probable that mercury is not harmful but these long and mild courses bear the stamp of latency producers. Mercury should be reserved for the old cases, the failures of a better treatment."

With all respect to the gallant Commander there is another point of view which deserves consideration. It is generally recognized that mercury, while inferior to arsenic as a spirochaetocide *en masse*, and slower in its action, yet has a certain power of permeating tissue that arsenic does not seem to possess. Arsenic has been compared to a barrage of shrapnel from field guns which quickly destroys all troops in the open but cannot reach those in the trenches and dug-outs. Mercury is comparable to the bombers and bayonet men who follow up the barrage and proceed to "mop up" the trenches and dug-outs and kill all the enemy who occupy them. According to this view a prolonged bombardment with arsenic only makes the inaccessible spirochaetes dig themselves in more securely so that it is necessary to use mercury as a "mopper up"

between barrages. This is the idea behind the continued treatment with both arsenic and mercury.

I have examined the records of several hundreds of cases at the Montreal General Hospital and Dispensary, and it is very rarely that a primary or secondary case fails to clear up both clinically and serologically under combined arsenic and mercury treatment, the failures being mostly due to interrupted treatment. I think the results from the combined treatment are quite as good as those from the use of arsenicals alone, and at any rate it does not seem wise to abandon a remedy which has proved its usefulness for so long a time in favour of one which is as yet, after all, more or less a trial.

To conclude this rather general discussion of the subject I will read a summary of a paper by Solomon of Harvard<sup>8</sup> on the treatment of neuro-syphilis: "The problem is to destroy the spirochaetes in the nervous system. The nervous tissue is walled off from the general body structures and this leads to a relative impermeability of drugs placed in the general circulation. However, some penetration does take place, the amount apparently varying in different individuals. Some cases react well to mild systemic treatment, others require more intensive treatment. There are many however who do not react to systemic treatment with arsphenamine, mercury or iodides. Some of them do well when medicaments are given directly into the cerebro-spinal fluid (Swift Ellis' treatment) or when special drainage is used. Theoretically, it seems advisable to place the medicament as near the site of patho-

logical change as possible, utilizing the lumbar subarachnoid space, the region of the cisterna magna and the ventricles as conditions indicate. It is more difficult on the whole to get satisfactory results in cases of tabes and general paresis than in the cases of the meningo-vascular type; the former usually require quite intensive treatment. There still remains a group of cases that cannot be satisfactorily modified by treatment with arsenic mercury, iodides or blood serum.

The immunity of the patient plays a large rôle in the results obtained and various procedures that may increase the immunity responses have a place in the treatment of neuro-syphilis. Some favourable reports have been made of the results obtained from inducing febrile reactions by inoculations with malaria and relapsing fever. The hopes for the future rest either on the methods of inducing greater immunity on the part of the patient, or on the discovery of drugs with greater power of permeation into the nervous system, such as as tryparsamide."

#### REFERENCES

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**Carbon Tetrachlorid Poisoning.**—B. M. Phelps, Almirante, Panama, and C. H. Hu, Boston, report two fatal cases of carbon tetrachlorid poisoning with their important pathologic findings, and also a series of animal experiments that tend to confirm the general view already held that carbon tetrachlorid may cause central necroses of the liver, and suggest that the same drug may cause necrosis of the suprarenal cells. In the two fatal cases of carbon tetrachlorid poisoning reported, the chief pathologic finding was central necrosis of liver. In one case, the suprarenal glands showed necrosis of the cortical cells. The

suprarenal glands of the other case were not preserved. Carbon tetrachlorid produces central necrosis of the liver and necrosis of the suprarenal cortex in guinea-pigs. Regeneration of liver cells following central necrosis is very rapid. It is suggested that the symptoms following ingestion of the drug in human cases are probably associated with the presence of central necrosis of the liver, and the absence of this lesion in the previously reported cases is probably due to the rapid regeneration of the liver cells.—*Jour. Am. Med. Assoc.*, April 19, 1924.